Immune-related nephritis, ureteritis and cystitis secondary to immune checkpoint inhibitors: A case report and review of the literature

GUANGQUAN ZHANG[1*], SILU XU[2*], JING WU[1], QIANQIAN GAO[3], YANZHI BI[4] and MIN XIAO[4]

[1]Department of Pharmacy, Changzhou Tumor Hospital, Changzhou, Jiangsu 213032, P.R. China; [2]Department of Pharmacy, Jiangsu Cancer Hospital/Jiangsu Institute of Cancer Research/The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu 210009, P.R. China; [3]Department of Pathology, Changzhou Tumor Hospital, Changzhou, Jiangsu 213032, P.R. China; [4]Department of Oncology, Changzhou Tumor Hospital, Changzhou, Jiangsu 213032, P.R. China

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Abstract. Immune checkpoint inhibitors (ICIs) have beneficially impacted cancer therapy but are frequently associated with immune-related adverse events (irAEs), most commonly affecting the skin and gastrointestinal system. By contrast, genitourinary toxicities are rare and often underrecognized. The present case report outlines a 62-year-old male with metastatic colorectal cancer who developed pan-urinary tract irAEs (concurrent immune-related nephritis, ureteritis and cystitis) after exposure to three distinct classes of ICIs. The patient initially experienced pollakiuria, urinary urgency, dysuria and hematuria, which worsened after switching to cadonilimab and adebrelimab. This deterioration coincided with rising serum creatinine levels and lack of improvement with antibacterial treatment. Urinalysis revealed leukocyturia and hematuria, while imaging demonstrated bilateral hydroureteronephrosis and diffuse bladder wall thickening. A multidisciplinary evaluation led to the diagnosis of ICI-induced pan-urinary tract irAEs. Both urinary symptoms and renal function resolved rapidly after halting immunotherapy and starting glucocorticoid treatment, with no recurrence during follow-up. In addition, a comprehensive review of reported cases was conducted to characterize this rare irAE presentation and further propose both diagnostic criteria and management strategies to facilitate early detection and effective treatment.

Correspondence to: Dr Min Xiao or Dr Yanzhi Bi, Department of Oncology, Changzhou Tumor Hospital, 68 Honghe Road, Xinbei, Changzhou, Jiangsu 213032, P.R. China
E-mail: xiaomin2290@sina.com
E-mail: biyanzhi222@163.com

*Contributed equally

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Introduction

Immune checkpoint inhibitors (ICIs) exert their antitumor effects through the blockade of inhibitory immune checkpoints, thereby reactivating T-cell-mediated immune responses against malignant cells (1). Their increasing clinical application has markedly improved survival outcomes in patients with advanced colorectal cancer, with a median progression-free survival time of 39.3 months for monotherapy (2). However, this therapeutic progress is accompanied by the growing recognition of immune-related adverse events (irAEs) as notable clinical complications (3). irAEs can affect almost any organ system, with dermatologic, gastrointestinal and hepatic toxicities being among the most common manifestations (4). By contrast, urinary tract irAEs are relatively rare, with immune-related acute kidney injury occurring in ~2.2-5.0% of patients. Furthermore, immune-mediated ureteritis and cystitis are also uncommon and have only been reported in isolated case reports (5-7). Currently, the prescribing information for cadonilimab and adebrelimab does not list ureteritis or cystitis as recognized adverse effects, increasing the likelihood of clinical under-recognition and delayed intervention (8). In addition, existing guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) do not offer specific recommendations for the diagnosis or management of immune-related ureteritis or cystitis (9,10), creating a key gap in guidance for clinicians. The present case report outlines a rare case of pan-urinary tract irAEs manifesting as concurrent nephritis, ureteritis and cystitis in a patient with advanced colorectal cancer following sequential ICI therapy. The present comprehensive report aims to provide a reference for clinical treatment and management of these unusual irAEs.

Case report

In 2015, the present patient, a 62-year-old male, was initially diagnosed with colon cancer and underwent a left hemicolectomy at the Department of General Surgery, Shanghai East Hospital (Shanghai, China), followed by 6 cycles of

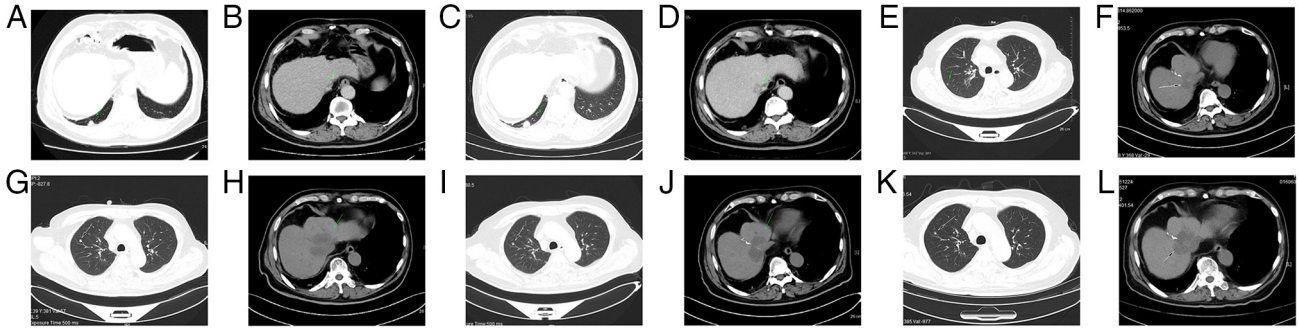

Figure 1. CT images of the primary tumor and metastatic lesions of the patient during the clinical course. (A and B) January 2024: Scattered solid pulmonary nodules (largest ~1.3 cm) and a low-density lesion adjacent to the right hepatic vein. (C and D) April 2024: Numerous scattered solid pulmonary nodules (largest ~1.7 cm), some increased in size; liver lesions unchanged. (E and F) January 2025: Shrunken low-density lesion near the first hepatic hilum and new lung metastases. (G and H) April 2025: 4.8 cm low-density lesion at the first hepatic hilum; multiple lung metastases, largest pulmonary nodule (1.4 cm) increased. (I and J) June 2025: Slightly smaller low-density lesion at the first hepatic hilum; two lung metastases unchanged. (K and L) December 2025: Low-density lesion at the first hepatic hilum (stable); two lung metastases unchanged.

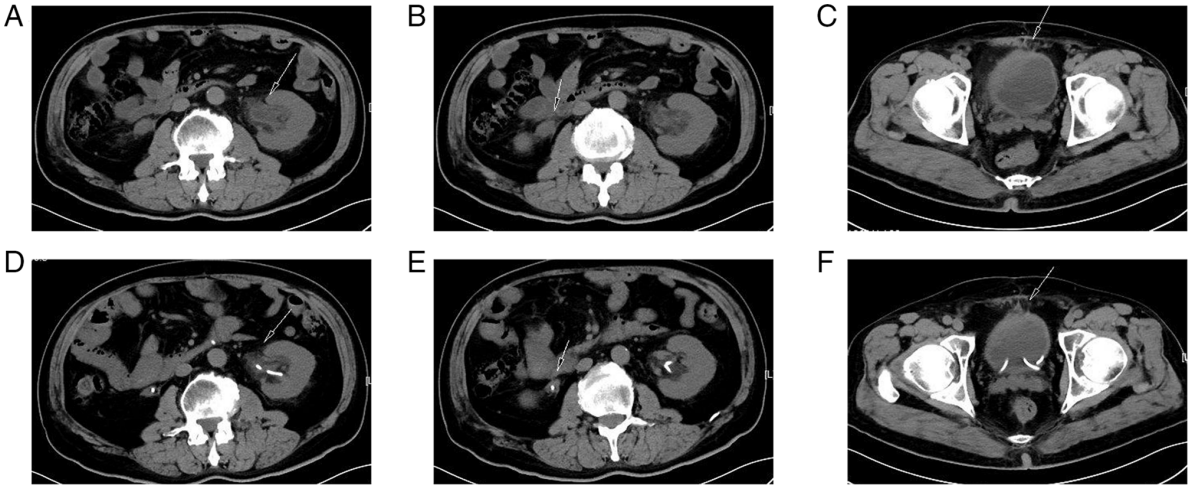

Figure 2. Comparison of urinary system CT findings before and after glucocorticoid therapy. (A-C) CT images of the urinary system obtained in April 2025, prior to initiation of glucocorticoid treatment, showing bilateral hydronephrosis, ureteral dilation and bladder wall thickening (black arrow). (D-F) CT images in June 2025 following glucocorticoid therapy, demonstrating marked resolution of hydronephrosis and ureteral dilation, along with improvement in bladder wall thickening (black arrow).

adjuvant chemotherapy (regimen unspecified). Post-treatment surveillance indicated stable disease.

In January 2020, a PET/CT scan revealed metastatic lesions in the liver, leading to a right hepatectomy, lysis of intestinal adhesions and cholecystectomy at the Department of Hepatobiliary Surgey, Shanghai East Hospital (Shanghai, China). Histopathological examination demonstrated moderately differentiated adenocarcinoma consistent with metastatic colorectal cancer. Immunohistochemical profiling of the liver metastasis showed cytokeratin 20^{+}, Ki-67 (20%$^{+}$), $HER2^{-}$, MutL homolog 1^{+}, MutS homolog (MSH)-2^{-}, $MSH6^{-}$, PMS1 homolog 2^{-}, $CDX2^{+}$ and carcinoembryonic antigen $(CEA)^{+}$, demonstrating mismatch repair deficiency. From May 2020, the patient completed 6 cycles of adjuvant XELOX chemotherapy (oxaliplatin + capecitabine) in the Department of Oncology, Changzhou Tumor Hospital (Changzhou, China) with subsequent follow-ups exhibiting continued disease stability. However, in April 2022, an abdominal CT scan revealed radiographic evidence of disease progression. The patient then received 6 cycles of bevacizumab in combination with XELOX, followed by maintenance therapy with bevacizumab and capecitabine. The medical history of the patient included chronic hepatitis B infection, essential hypertension and a history of smoking. The patient exhibited no other marked chronic comorbidities. Baseline laboratory assessments exhibited a urine white blood cell (WBC) count of 0.9/μl (reference range: 0-25/μl) and red blood cell (RBC) count of 7.3/μl (reference range: 0-23/μl). The serum creatinine level was 69.8 μmol/l (reference range: 57-111 μmol/l) and creatinine clearance was calculated at 127.8 ml/min. Baseline imaging of the urinary system revealed no abnormalities in the kidneys, ureters or bladder.

In January 2024, a routine surveillance chest and abdominal CT scan revealed progression of bilateral pulmonary metastases (Fig. 1A and B). As a result, the patient commenced immunotherapy with tislelizumab (200 mg on day 1) in combination with regorafenib (160 mg orally, once daily from days 1-21). The regimen was well-tolerated, with no marked treatment-related adverse effects reported. In April 2024, a CT scan showed stable disease in the patient (Fig. 1C and D). A further 13 days

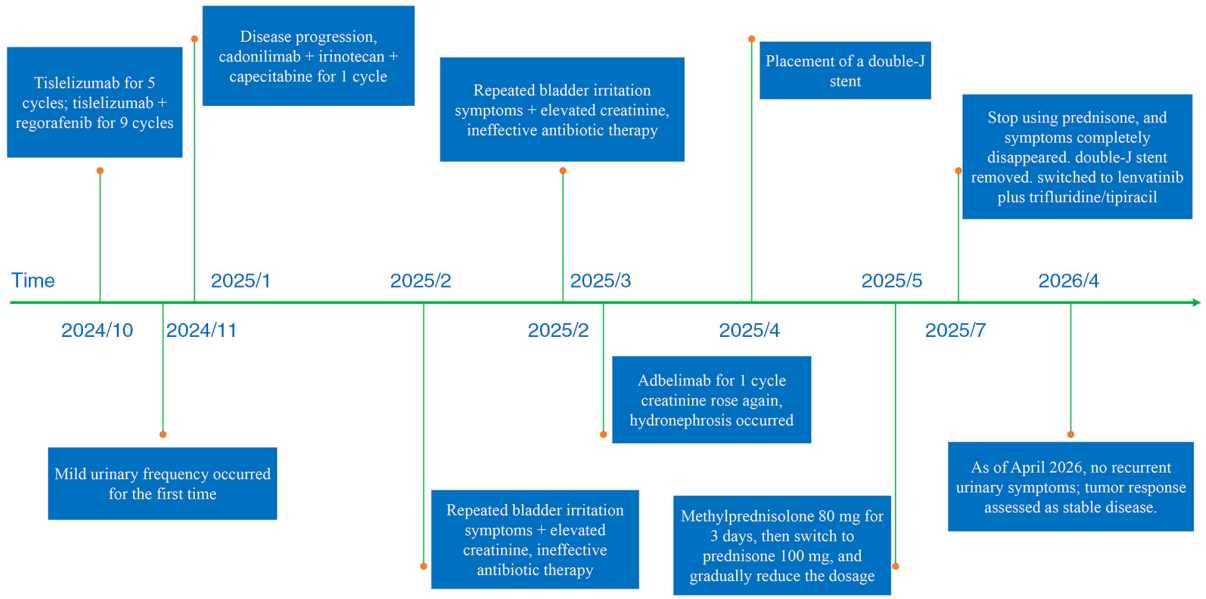

Figure 3. Timeline of anti-tumor therapy and the development of immune checkpoint inhibitor-related nephritis, ureteritis and cystitis.

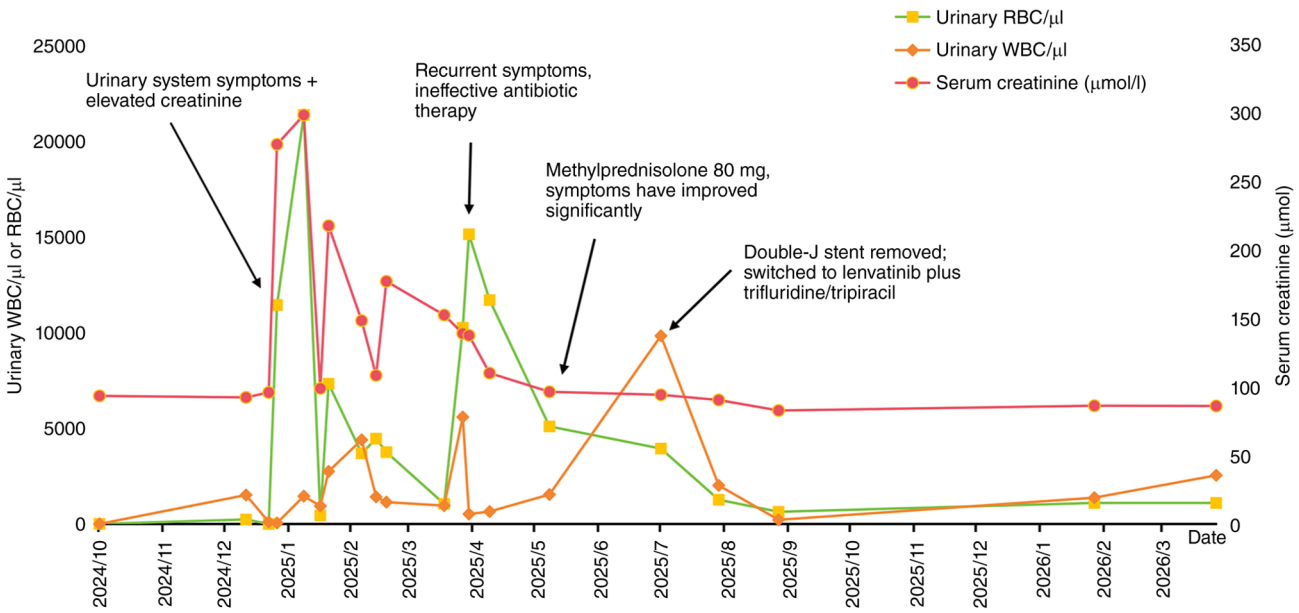

Figure 4. Changes in urinary RBC/WBC counts and serum creatinine. RBC, red blood cell' WBC, white blood cell.

after receiving the 14th cycle of tislelizumab (in November 2024), the patient developed mild lower urinary tract symptoms, including urinary frequency, urgency and dysuria. These symptoms were initially attributed to benign prostatic hyperplasia and showed partial improvement following treatment with tamsulosin and Traditional Chinese Medicine (Relinqing granules). However, after the 15th cycle of tislelizumab, urinalysis revealed markedly elevated WBC (1,515.3/μl) and RBC (237.6/μl) counts. Despite empirical treatment with levofloxacin, no clinical improvement was observed and no further targeted interventions were initiated at that point. In January 2025, due to CT finding indications of disease progression relative to previous imaging (Fig. 1E and F), the treatment regimen was escalated to chemo-immunotherapy consisting of cadonilimab (500 mg on day 1), irinotecan (400 mg on day 2) and capecitabine (1,500 mg twice daily from days 1-14). A further 9 days after the first administration of cadonilimab, the patient experienced worsening of lower urinary tract symptoms, accompanied by gross hematuria. Urine examination revealed marked pyuria (WBC count: 21,397.4/μl) and hematuria (WBC count: 1,455.3/μl), accompanied by acute kidney injury (serum creatinine: 299.0 μmol/l). Despite these findings, complete blood counts and inflammatory markers including WBC count, C-reactive protein and procalcitonin remained within the normal limits. Repeated urine cultures consistently returned negative results throughout the observation period. Abdominal CT imaging revealed bilateral hydroureteronephrosis and diffuse thickening of both ureteral and bladder

Table I. Naranjo assessment scale of ICI-related nephritis, ureteritis and cystitis.

Related issue	Standard for evaluation				Justification for score
	Yes	No	Unknown	Score	
Are there previous conclusive reports on this reaction?	+1	0	0	+1	Mentioned in the literature
Did the adverse event occur after administration of the suspected drug?	+2	-1	0	+2	irAEs developed following ICI therapy
Did the reaction improve upon discontinuation of the drug or administration of a specific antagonist?	+1	0	0	+1	Improved after drug discontinuation
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+2	Recurred after switching ICIs
Are there other plausible explanations (unrelated to the drug) that could independently account for the reaction?	-1	+2	0	-1	Urinary tract infection or tumor
Did the reaction reappear when a placebo was given?	-1	+1	0	0	Placebo not administered
Was the drug present in the blood or other bodily fluids at concentrations known to be toxic?	+1	0	0	0	Not tested
Did the severity of the reaction increase with a higher dose or decrease with a lower dose?	+1	0	0	0	No dose adjustment was made
Has the patient experienced a similar reaction to the same or a related drug in the past?	+1	0	0	+1	Recurrent episodes after switching to different ICIs
Was the adverse event determined by any objective evidence?	+1	0	0	+1	Laboratory and imaging findings
Total score			7		

Score <0, doubtful; 1-4, possible; 5-8, probable; and >9, definite. ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events.

walls (Fig. 2A-C). Due to marked thrombocytopenia, invasive diagnostic procedures such as cystoscopy and renal biopsy were too high-risk owing to an elevated chance of bleeding. Despite immunotherapy being temporarily withheld and the patient being treated empirically with piperacillin-tazobactam, there was no marked clinical improvement in genitourinary symptoms. Notably, follow-up urinalyses demonstrated a gradual decline in WBC and RBC counts, accompanied by normalization of serum creatinine, indicating renal function recovery. In February 2025, systemic chemotherapy was discontinued and the patient was transitioned to monotherapy with carbognilumab. Shortly thereafter, the patient developed recurrent lower urinary tract symptoms accompanied by a decline in renal function, with serum creatinine rising to 218.4 μmol/l. Urine culture determined the presence of *Escherichia coli* and although targeted antibiotic therapy was initiated, the symptoms remained unresponsive. As a result, immunotherapy was temporarily halted, leading to a gradual improvement in clinical symptoms. In March 2025, the patient received a dose of adebrelimab (1,200 mg on day 1). This was followed by a recurrence of lower urinary tract symptoms and the development of bilateral hydronephrosis. Bilateral ureteral stent placement was performed, which led to improved renal function. In April 2025, CT scan showed tumor progression but no further anti-tumor treatment was administered due to irAEs (Fig. 1G and H). The antineoplastic treatment course of the patient and the occurrence of urinary irAEs is summarized in Fig. 3. Following a multi-disciplinary treatment (MDT) meeting, a provisional diagnosis of ICIs-related urinary irAEs was established. According to the Common Terminology Criteria for Adverse Events, the patient was classified as immune-related nephritis (grade 3) and immune-related ureteritis/cystitis (grade 3) (11).

In May 2025, methylprednisolone treatment was initiated at 80 mg/day (equivalent to prednisone 1.18 mg/kg/day) for 3 days, followed by sequential administration of oral prednisone at 100 mg/day for 2 days. This regimen led to the marked alleviation of symptoms, with marked improvements in urinary frequency, urgency, dysuria and gross hematuria, as well as a return to baseline levels in repeat renal function tests. The prednisone dosage was subsequently tapered by 20 mg every 3 days and complete resolution of the bladder irritation symptoms observed 1 week later. In late May, the patient's treatment was changed to oral prednisone at 30 mg/day, followed by weekly reductions of 5 mg until a maintenance dose of 10 mg/day was reached. The temporal trends of urinary WBC/RBC counts and serum creatinine throughout the course of immunotherapy are illustrated in Fig. 4. After 6 weeks of corticosteroid therapy, follow-up CT imaging of the urinary system exhibited notable resolution of hydronephrosis and proximal/mid-ureteral dilation, as well as improvement in bladder wall thickening (Fig. 2D-F). The stent was removed on in July 2025, due to potential complications (bladder irritation and low back pain). After halting immunotherapy, the patient received lenvatinib + trifluridine/tipiracil. Through comprehensive evaluation using the Naranjo assessment scale and MDT discussion, the patient was definitively diagnosed with ICI-related nephritis/ureteritis/cystitis (12). After recovery from irAEs, the patient underwent regular follow-up for 1 year. The last laboratory assessments during follow-up showed a urine white blood cell count of 1102.6/μl (reference range, 0-25/μl) and a red blood cell count of 2545.8/μl (reference range, 0-23/μl), and the serum creatinine level was 71.9 μmol/l (reference range, 57-111 μmol/l) (Fig. 2), with no recurrence of urinary symptoms such as frequency, urgency or dysuria. Concurrently, as of December 2025, repeat tumor evaluations showed stable disease (Fig. 1I-L). From 2026 onward, although the patient refused routine CT scans due to personal financial reasons, the CEA levels remained generally stable, suggesting that tumor control remained favorable.

Discussion

Within the present report, a case of recurrent immune-related nephritis, ureteritis and cystitis is reported in a patient with advanced colorectal cancer who received sequential treatment with three ICIs (tislelizumab, cadonilimab and adebrelimab). During the initial combination therapy with tislelizumab and regorafenib, the patient developed symptoms of mild lower urinary tract irritation. These symptoms progressed markedly, along with rising serum creatinine levels after transitioning to cadonilimab monotherapy, demonstrating a clear temporal association between drug administration and symptom onset. Temporary suspension of immunotherapy without corticosteroid intervention resulted in gradual resolution of urinary symptoms and normalization of creatinine levels, suggesting that irAEs affecting the urinary system may demonstrate self-limiting characteristics (13). However, urinary tract irritation symptoms re-emerged following subsequent administration of adebrelimab.

Throughout the 6-month treatment period, serial urine cultures remained persistently negative, with the exception of a single episode of *Escherichia coli* isolation. Notably, the patient exhibited minimal clinical improvement despite a number of adjustments in antibiotic therapy. Imaging studies including abdominal ultrasonography and urinary cytology ruled out malignancy, urolithiasis and benign prostatic hyperplasia. CT imaging of the urinary tract revealed bilateral hydronephrosis, proximal and mid-ureteral dilation, circumferential ureteral wall thickening and irregularity, as well as diffuse bladder wall thickening with all findings consistent with extensive urinary tract inflammation. Symptom resolution following corticosteroid administration, in conjunction with clinical, laboratory and radiographic evidence, determined the diagnosis of immune-related ureteritis and cystitis. In addition, the patient experienced an almost 3-fold increase in serum creatinine from baseline at the onset of urinary symptoms, followed by the development of bilateral hydronephrosis, suggestive of acute kidney injury. Based on the absence of a history of dehydration, hemorrhage or cardiac dysfunction, prerenal causes of acute kidney injury were initially excluded. Although a renal biopsy could not be performed due to thrombocytopenia, intrarenal etiologies (renal causes) could not be definitively ruled out. Imaging evidence of ureteral wall thickening and dilation suggested functional obstruction, pointing to a postrenal component of acute kidney injury. However, a multifactorial mechanism involving both intrinsic renal injury and postrenal obstruction remains a likely explanation. Notably, the symptoms and renal function of the patient improved markedly following glucocorticoid therapy. In the absence of

Table II. Clinical profiles of patients with immune-related nephritis, ureteritis and cystitis reported in the literature.

First author, year	Age/ sex	Carcinoma	ICI (no. cycles)	Symptoms	Scr, μmol/l	Urinalysis	Urine culture	Cystoscopy	Imaging examination	Treatment	Re-challenge	(Refs.)
Ji *et al*, 2024	55/ male	Gastric cancer	Sintilimab (3)	Renal colic hematuria hydronephrosis	126.0	Elevated WBC/RBC	Negative	Swollen and ulcerative bladder mucosa	Hydronephrosis, dilation renal pelvis, thickened ureter wall and bladder wall	Bilateral ureteral stenting	No	(13)
Tu *et al*, 2021	53/ male	Lung cancer	Sintilimab (3)	Haematuria pollakiuria painful micturition pain	299.0	Elevated WBC/RBC	Negative	Diffused redness of bladder mucosa	Thickened bladder, hydronephrosis lower back and dilated ureter	MP, 1 mg/ kg/day	No	(16)
Li *et al*, 2023	49/ male	Esophageal carcinoma	Tislelizumab (6)	Gross hematuria pollakiuria painful micturition lower back pain	211.0	Elevated WBC/RBC and proteinuria 3+	Negative	Diffused redness of the bladder mucosa	Mild hydronephrosis, dilated ureter and thickened bladder wall	MP, 60 mg; symptom recurrence after rapid dose reduction	No	(17)
	49/ male	Gastric cancer	Nivolumab (2)	Hematuria pollakiuria painful micturition fever	190.0	Elevated WBC/RBC and proteinuria 3+	Negative	None	Mild hydronephrosis, dilated ureters and thickened bladder wall	MP, 60 mg; symptom recurrence after rapid dose reduction	No	
Zhang *et al*, 2024	72/ male	Lung cancer	Pembroli zumab (6)	Urinary frequency nocturia gross hematuria bilateral flank pain	169.7	Elevated WBC/RBC	Negative	Diffuse erythema, marked local edema and follicular hyperplasia, with floating mucosa in the bladder	Mild bilateral hydroureterosis	MP, 40 mg; symptom recurrence after rapid dose reduction	Yes, failed	(18)
Present study	62/ male	Colon cancer	Tislelizumab, cadonilimab and adebelimab (16)	Pollakiuria urinary urgency dysuria hematuria	299.5	Elevated WBC/RBC and proteinuria 3+	Positive	None	Hydronephrosis, dilated ureter and thickened bladder wall	MP, 100 mg	Yes, failed	-

ICI, immune checkpoint inhibitor; Scr, serum creatinine; WBC, white blood cell; RBC, red blood cell; MP, methylprednisolone.

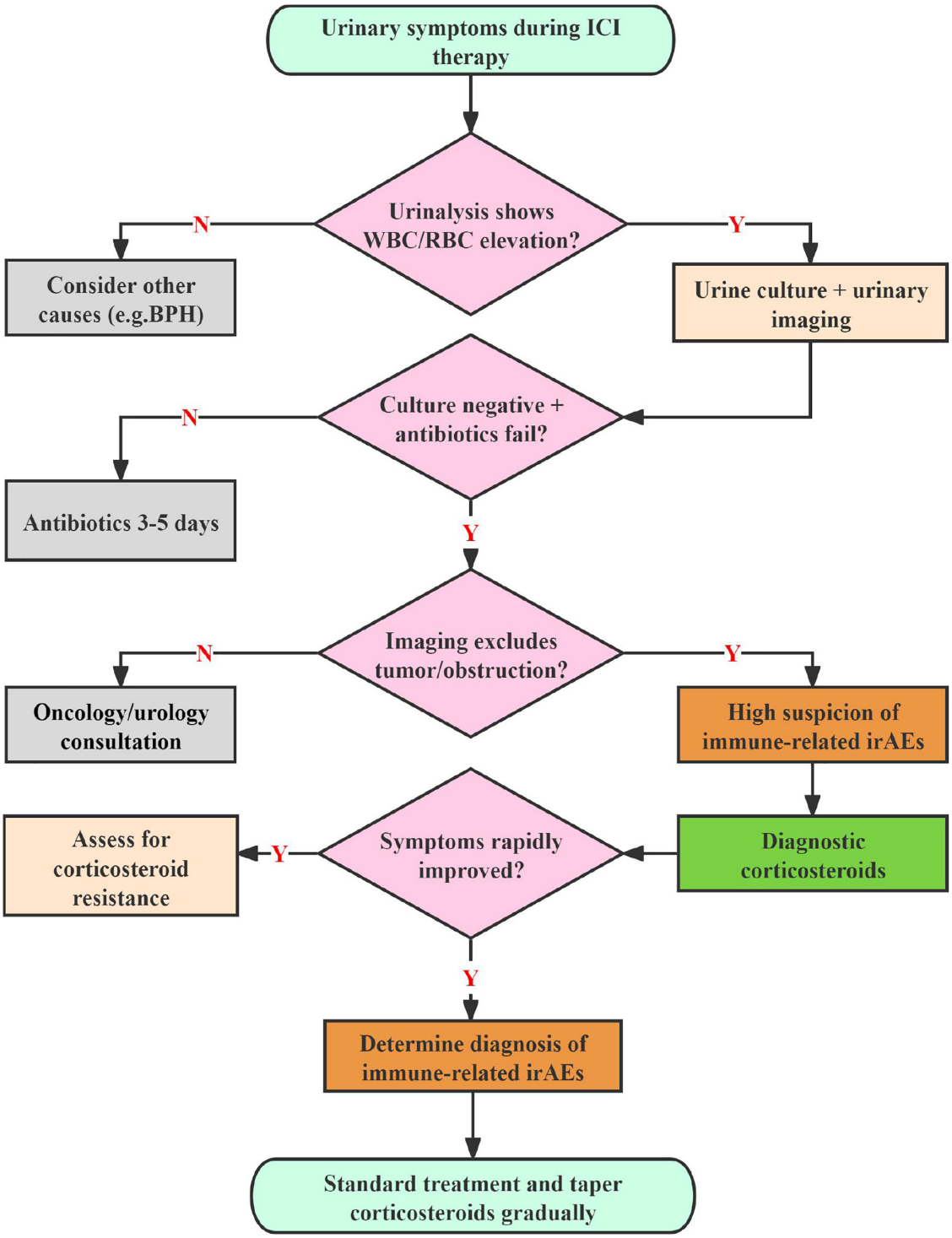

Figure 5. Diagnostic algorithm for suspected urinary immune-related adverse events. ICI, immune checkpoint inhibitor; WBC, white blood cell; RBC, red blood cell; irAE, immune-related adverse events; BPH, benign prostatic hyperplasia; N, no; Y, yes.

histopathological evidence, this rapid response may represent evidence to support immune-mediated kidney injury.

At present, the lack of validated biomarkers or standardized diagnostic criteria for urinary irAEs necessitates a diagnosis of exclusion in clinical settings. In this case, the favorable response of the patient to glucocorticoid therapy supported the diagnosis of ICI-related nephritis, ureteritis and cystitis. To assess the causal association between immunotherapy and the observed urinary irAEs, the Naranjo Adverse Drug Reaction Probability Scale was applied, evaluating all 10 items according to established guidelines (Table I). The patient received a total score of 7, indicating a probable association between the ICIs and the urinary irAEs. Notably, ureteritis and cystitis represent atypical manifestations of irAEs that are not currently listed in the prescribing information for either cadonilimab or adebrelimab. Given the sequential exposure to three different ICIs, it is not possible to definitively attribute the urinary irAEs to a single agent. Instead, it remains plausible that all three

ICIs may have contributed to the development of this rare complication.

Epidemiological data indicate that irAEs involving the urinary tract, while rare, are recognized complications of ICI therapy (14). Among these, renal irAEs are the most common, with acute interstitial nephritis being the predominant histopathological finding. Less frequently, glomerulonephritis and acute tubular necrosis have also been reported (15). By contrast, irAEs affecting the ureter and bladder are markedly rare, with existing evidence limited to isolated case reports. The present case is a rare instance of simultaneous irAEs involving numerous segments of the urinary tract including the kidneys, ureters and bladder, an occurrence that has been scarcely documented in the literature. To assess the prevalence of such cases, a systematic search of PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://www.webofscience.com) and the China National Knowledge Infrastructure (https://www.cnki.net) from inception to March 31, 2025, was conducted, using the following keywords: 'Immune checkpoint inhibitors', 'immune-related adverse events', 'ureteritis', and 'cystitis'. The systematic literature review identified only 5 cases of concurrent acute kidney injury, with detailed findings summarized in Table II (13,16-18). Patients were all male, with ages ranging from 49-72 years, with males representing 100.0% (6/6) of the cohort. The onset of urinary irAEs occurred between 2-16 treatment cycles following ICI initiation, with the majority (5 cases, 83.3%) manifesting within 2-6 cycles. Primary tumors included lung cancer (n=2), gastric cancer (n=2), esophageal carcinoma (n=1) and colon cancer (n=1). Among the 6 cases, cystitis was reported in all, ureteritis in 5 cases and nephritis in only 1 case. This uneven distribution likely reflects both the under-recognition of concurrent nephritis in patients presenting with ureteritis or cystitis and the absence of standardized diagnostic criteria for urinary tract irAEs, which may contribute to inconsistent identification and reporting.

A synthesis of previously reported cases, along with the clinical course of the current patient, highlighted a set of consistent features: Pollakiuria, urinary urgency, dysuria, gross hematuria, hydronephrosis, lumbago and elevated serum creatinine levels. In all documented cases, urine cultures remained sterile despite marked pyuria and hematuria on urinalysis, suggesting a non-infectious inflammatory process rather than a conventional urinary tract infection. It may therefore be proposed that in patients undergoing ICI therapy, the presence of urinary tract symptoms with elevated serum creatinine, negative microbiological testing and poor response to antibiotics should prompt immediate consideration of immune-related nephritis, ureteritis or cystitis. The patient exhibited persistent irAEs involving the urinary tract. All serial urine cultures were found to be sterile, apart from one *Escherichia coli*-positive specimen and there was no clinical improvement following antibiotic therapy, precluding a definitive differentiation between sterile pyuria and occult infection. When clinically feasible, it is recommended that metagenomic next-generation sequencing of the urine be performed in such patients to further screen for rare pathogens that are undetectable by conventional culture, thereby reducing the risk of misdiagnosis and inappropriate glucocorticoid use (19). Cystoscopy in a number of reported cases revealed diffuse bladder mucosal congestion, while histopathological findings were characterized by predominant lymphocytic and neutrophilic infiltration. However, these findings closely resemble those of conventional cystitis, limiting the diagnostic specificity of histopathology in distinguishing irAEs from other inflammatory conditions (16,17).

Cystoscopy or biopsy is not recommended for routine diagnostic assessment of patients with suspected immune-mediated cystitis, given the difficulties in distinguishing its inflammatory features from those of conventional cystitis, as well as the invasive nature and inherent diagnostic uncertainty of the procedure (20). The underlying pathogenesis of irAEs is hypothesized to stem from dysregulated immune activation, wherein aberrant immune responses mistakenly target normal tissues, leading to a cascade of inflammatory events. Although the precise mechanisms of ICI-associated nephro-urinary toxicity remain unclear, proposed contributing factors include impaired immune tolerance, abnormal activation of tissue-resident T cells and autoantibody production, potentially acting synergistically (21). The present case is particularly notable for the rare simultaneous involvement of the kidney, ureter and bladder, as these organs are typically affected independently by irAEs (22). The concurrent manifestation suggests the possibility of shared immunological pathways across urinary tract tissues, though further research is needed to elucidate the exact mechanistic connections.

Current NCCN and ESMO guidelines do not provide standardized treatment protocols specifically for immune-related ureteritis and cystitis. However, both sets of guidelines emphasize that early initiation of corticosteroid therapy remains an established method of management for the majority of irAEs. The clinical guidelines for nephrotoxicity advise permanent discontinuation of ICIs in cases of grade 3 nephrotoxicity. The recommended initial corticosteroid regimen should consist of prednisone or methylprednisolone at 1-2 mg/kg/day or methylprednisolone pulse therapy at 250-500 mg/day for 3 days. In addition, urinary protein and serum creatinine levels should be monitored every 3-7 days. Once the toxicity resolves to grade 1, corticosteroid administration may be gradually tapered over 4-6 weeks. At present, the key therapeutic goals in managing urinary irAEs are to preserve renal function and relieve urinary symptoms. However, the recommended initial dosing and tapering strategies for immune-mediated ureteritis/cystitis are derived primarily from individual case studies. In all 6 cases reported, patients experienced marked improvement in urinary symptoms following corticosteroid therapy and discontinuation of immunotherapy. This clinical response was supported by normalization of serum creatinine and gradual resolution of pyuria and hematuria, reinforcing the effectiveness of corticosteroids in treating urinary tract irAEs. In steroid-refractory cases, second-line immunosuppressive agents such as infliximab (an anti-TNFα monoclonal antibody) may be considered (23). The majority of cases employed an initial corticosteroid dose of methylprednisolone at 1-2 mg/kg/day, which proved effective in controlling symptoms. However, 3 patients experienced a recurrence of symptoms following rapid corticosteroid tapering, highlighting the importance of a gradual dose reduction to prevent recurrence of irAEs (17,18). Therefore, the present report

recommends maintaining corticosteroid therapy until urinary irAEs resolve to grade 1 severity, followed by a gradual taper over a minimum of 4-6 weeks to minimize relapse risk. For grade 3 renal irAEs, NCCN guidelines advise conducting a careful risk-benefit assessment before considering reinitiation of ICIs. If renal function normalizes and symptoms improve to grade ≤1, ICIs may be cautiously resumed either without corticosteroids or with maintenance low-dose prednisone (10 mg/day), preferably using an alternative ICI class to reduce the risk of recurrence. Among the cases reviewed, only 1 patient underwent ICI rechallenge, but re-treatment was unsuccessful, underscoring the marked risk of therapeutic failure following urinary tract irAEs. Given that the rechallenge failure rate for grade ≥3 whole-urinary-tract irAEs appears to be higher compared with that for irAEs affecting other organs, permanent discontinuation is recommended in accordance with current guidelines. In the present case, the patient initially tolerated monotherapy with the programmed cell death protein 1 (PD-1) inhibitor tislelizumab without complications. However, progression to combination therapy with the PD-1/cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) bispecific antibody cadonilimab triggered severe urinary irAEs. Notably, these symptoms recurred even after switching to a PD-L1 inhibitor (adebrelimab). The persistence of urinary irAEs despite sequential treatment with ICIs targeting distinct immune checkpoints suggests that dual checkpoint blockade may induce a durable or irreversible state of T-cell hyperactivation. As a result, even subsequent monotherapy with PD-1 or programmed death-ligand 1 (PD-L1) inhibitors may be sufficient to provoke marked urinary tract inflammation (24). Previous epidemiological data have exhibited a notably higher incidence of irAEs with combination therapy involving PD-1/PD-L1 inhibitors and CTLA-4 inhibitors compared with PD-1/PD-L1 inhibitors alone (25). The mechanistic basis for this difference may be because CTLA-4-mediated negative regulation of the immune response occurs at an early stage of immune activation; consequently, immune-related toxicities resulting from CTLA-4 inhibition tend to be more severe. This may explain why the present patient experienced a dramatic escalation of urinary irAEs after the switch from tislelizumab to cadonilimab. Furthermore, both PD-1 and CTLA-4 are key negative checkpoint regulators of T-cell activation and their simultaneous blockade may lead to synergistic activation of the immune response, thereby notably lowering the threshold for T-cell activation and amplifying the intensity of the immune response (26). Therefore, the risk of urinary irAEs cannot be completely excluded in patients receiving bispecific antibody therapy, even in those who have previously tolerated anti-PD-1 monotherapy and enhanced monitoring during treatment is warranted.

To the best of our knowledge, at present, there are no validated biomarkers to predict the risk or enable early detection of urinary tract irAEs. Based on the present case findings and a comprehensive review of the literature, it may bed concluded that the diagnosis of immune-related nephritis, ureteritis and cystitis primarily relies on the exclusion of alternative causes. The present evidence-based diagnostic and therapeutic protocol consists of the following elements: i) Baseline evaluation: Prior to initiating ICI therapy, patients should undergo thorough baseline assessments, including urinalysis, serum creatinine measurement and imaging of the urinary tract; ii) clinical suspicion: Urinary irAEs should be considered in patients on ICIs who present with urinary tract irritation symptoms and renal dysfunction, especially when urine cultures are sterile and symptoms do not improve with empirical antibiotic treatment; iii) exclusion of other causes: Diagnostic imaging and cystoscopy are key in excluding mechanical obstruction, malignancy, nephrolithiasis or infectious etiologies; iv) timely intervention: Early recognition and prompt initiation of treatment can reduce the duration of corticosteroid therapy and help avoid unnecessary use of antibiotics and analgesics; and v) rechallenge considerations: Due to the high failure rate of ICI rechallenge, permanent discontinuation is recommended in cases with grade 3 whole-urinary-tract irAEs. Based on the aforementioned clinical experience and literature evidence, the present report developed a diagnostic algorithm for suspected urinary irAEs presented in Fig. 5.

The present study exhibits a number of important limitations. First, cadonilimab and adebrelimab were employed as later-line treatments outside of standard guideline recommendations, primarily due to limitations in drug accessibility. Second, thrombocytopenia prevented the timely use of cystoscopy and renal biopsy in the present patient, resulting in a lack of histopathological determination for the suspected immune-related nephro-urinary toxicity.

Overall, although rarely life-threatening, immune-related nephritis, ureteritis and cystitis often result in severe urinary symptoms that notably diminish patient quality of life. At present, there are no standardized guidelines for the diagnosis and management of immune-related ureteritis and cystitis, contributing to frequent under-recognition during ICI therapy and delayed treatment, which may lead to worse clinical outcomes. The present report outlines a rare case of pan-urinary tract irAEs following sequential exposure to three different classes of ICIs and includes a systematic review of similar cases reported in the literature. In patients receiving ICI therapy who develop urinary symptoms alongside elevated serum creatinine, a prompt and thorough diagnostic workup is key. This should include urinalysis, renal function testing, imaging of the urinary tract, and diagnostic cystoscopy. After excluding urinary tract infections and malignancy, the possibility of urinary tract irAEs should be considered and corticosteroid therapy should be initiated without delay. The present report outlines the diagnostic rationale and therapeutic approach for immune-related nephritis, ureteritis and cystitis, with the aim of facilitating earlier recognition and appropriate management of these uncommon but impactful complications.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GZ and SX contributed to the drafting of the manuscript and the design of the present study. JW and QG performed a critical literature review and contributed to the acquisition, analysis and interpretation of data. GZ and MX contributed to the follow-up and data analysis. YB and MX contributed to the interpretation of data. YB and MX confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Changzhou Cancer Hospital (Changzhou, China; approval no. 2025-SR-NO.022).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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